Review

When neurogenesis encounters aging and disease

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In this review, we consider the evidence that a reduction in neurogenesis underlies aging-related cognitive deficits and impairments in disorders such as Alzheimer's disease (AD). The molecular and cellular alterations associated with impaired neurogenesis in the aging brain are discussed. Dysfunction of presenilin-1, misprocessing of amyloid precursor protein and toxic effects of hyperphosphorylated tau and β-amyloid probably contribute to impaired neurogenesis in AD. Because factors such as exercise, environmental enrichment and dietary energy restriction enhance neurogenesis, and protect against age-related cognitive decline and AD, knowledge of the underlying neurogenic signaling pathways could lead to novel therapeutic strategies for preserving brain function. In addition, manipulation of endogenous neural stem cells and stem cell transplantation, as standalone or adjunct treatments, seems promising.

Introduction

There is a progressive decline in the regenerative capacity of most organs with increasing age, resulting in functional deterioration and poor repair from injury and disease. Once thought to exist only in high-turnover tissues, such as the intestinal lining or bone marrow, it now appears that most tissues harbor stem cells that contribute to tissue integrity throughout life. In many cases, stem cell numbers decrease with age, suggesting that stem cell aging could be of fundamental importance to the biology of aging ([1] for review). Therefore, understanding the regulation of stem cell maintenance and/or activation is of considerable relevance to understanding the age-related decline in the maintenance of tissue integrity, function, and regenerative response.

The adult brain contains neural stem cells (NSCs) that self-renew, proliferate and give rise to neural progenitor cells (NPC) that exhibit partial lineage-commitment. Following several cycles of proliferation, NPC differentiate into new neurons and glia. NSCs are increasingly acknowledged to be of functional significance and harbor potential for repair of the diseased or injured brain. The dramatic decline in neurogenesis with age may contribute to impairments in learning and memory. Aging is also the greatest risk factor for Alzheimer's disease (AD), a neurodegenerative disease characterized by progressive loss of memory and cognitive decline. Alterations in neurogenesis have been described extensively in animal models of AD, and key proteins involved in AD pathogenesis have been shown to regulate neurogenesis. By understanding the molecular mechanisms underlying neurogenesis and its decline with aging it could become possible to manipulate NSCs to treat for brain disorders.

Neurogenesis in the adult mammalian brain

There are two neurogenic areas in the adult brain: the subventricular zone (SVZ) abutting the lateral ventricles, which contains NSCs that give rise to neurons in the olfactory bulb, and the subgranular layer (SGL) in the dentate gyrus (DG) of the hippocampus, in which NSCs become new granule cell neurons (Figure 1). Thus, the adult brain has more capacity for plasticity at the cellular level than was previously thought. The prevailing hypothesis holds that the putative NSCs of the SVZ are quiescent, glial fibrillary acidic protein (GFAP)-positive cells that share properties of astrocytes, referred to as type B cells ([2] for review). Type B cells give rise to transit-amplifying type C cells that are GFAP-negative. These intermediate progenitor cells (IPs or NPCs) give rise to polysialated neural cell adhesion molecule (PSA-NCAM)- and doublecortin (DCX)-expressing neuroblasts that migrate in chains through the rostral migratory stream (RMS) toward the olfactory bulb where they differentiate into either granule cells or periglomerular neurons [3] (Figure 1). Migration and maturation of adult neuroblasts has also been classified based on their electrophysiological properties [4,5].

Within the DG, newly formed neurons populate the inner third of the granule cell layer (GL). Two types of NSCs can be identified in the SGL according to their specific morphologies and expression of unique sets of molecular markers. Type I cells are similar to type B in the SVZ [6–8] and type II (nonradial) cells are similar to type C in the SVZ (Figure 1 [8]). Type I and II cells can be identified by distinct morphological and molecular markers (Figure 1). Newly formed neurons in the GCL send axonal projections to the CA3 subfield of the hippocampus and spineless dendrites to the molecular layer [9]. In the

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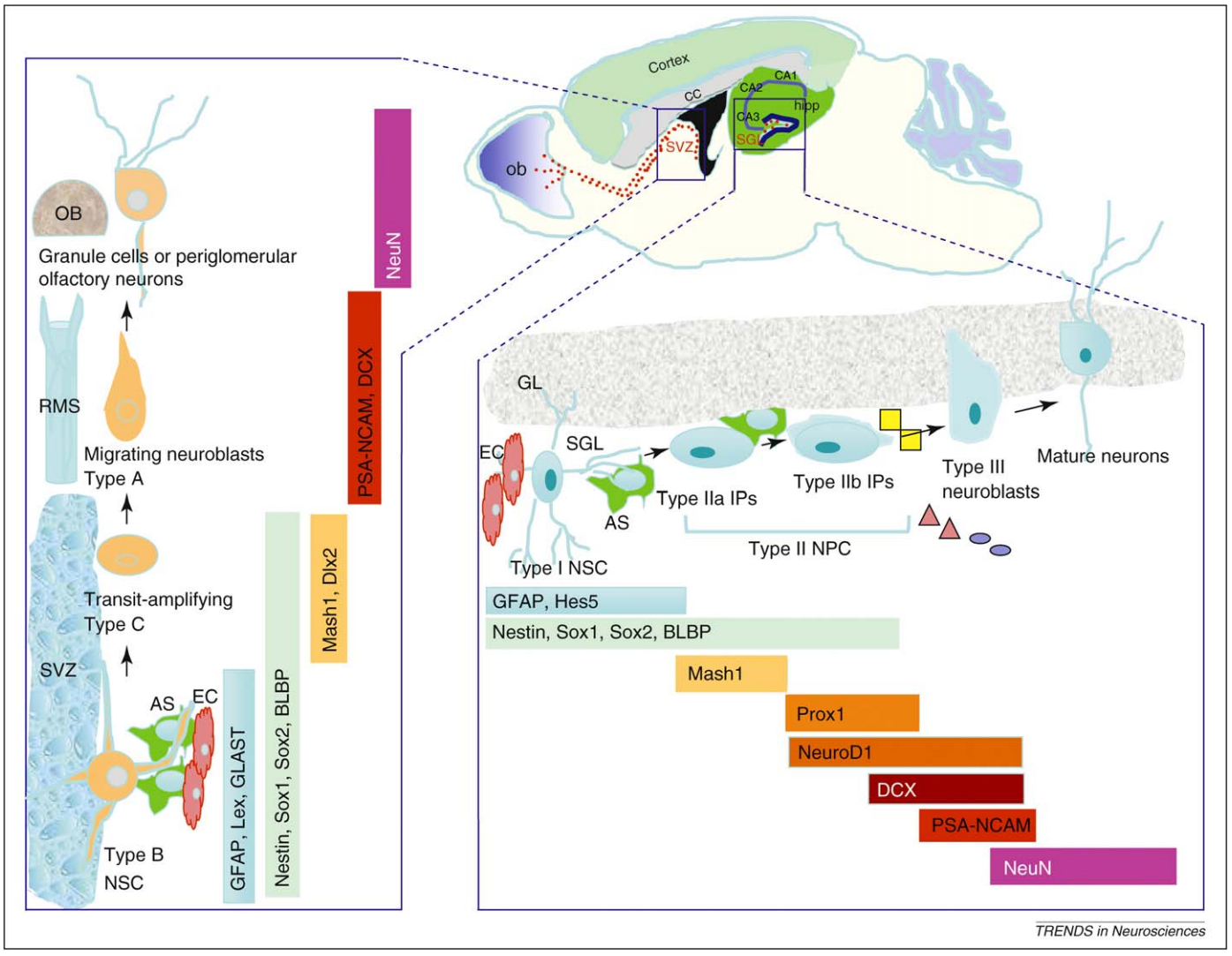

Figure 1. Neurogenesis in the adult rodent brain. Sagittal section of mouse brain showing the neurogenic microenvironments in the adult brain: the subventricular zone (SVZ) and the subgranular layer (SGL) of the dentate gyrus (DG). Stages of morphological and physiological development of neural stem cells (NSCs) in the SVZ (left) and SGL (right) are illustrated in inserts. Specifically, the SGL contains type I NSCs, and type II and type III progenitor cells which can be identified by distinct morphological and molecular markers. Type I have radial processes extending into the inner molecular layer. These cells express nestin, glial fibrillary acidic protein (GFAP), mammalian hairy and enhancer-of-split homologs (Hes5), brain lipid-binding protein (BLBP) and sex-determining region Y-box 1,2 (Sox1 and Sox2). This pool of NSCs stays relatively stable throughout life. Type II [neural progenitor cells (NPCs) or intermediate progenitors (IP)] have only short processes if any, and do not express GFAP. Type II cells could arise from type I cells. Type II cells can be divided to two subpopulations: **(i)** type IIa, which express Mash1 (Ascl1) as well as retaining expression of NSC markers such as Sox2, and **(ii)** type IIb cells, which are early-committed neuronal progenitors expressing the transcription factors prospero homeobox protein 1 (Prox1), neurogenic differentiation 1 (NeuroD1), as well as doublecortin (Dcx). They continue to proliferate and can give rise to type III cells, which are migratory neuroblasts that express DCX and polysialated neural cell-adhesion molecule (PSA-NCAM). After a limited number of cell divisions, type III cells exit the cell cycle and become mature granule neurons. Multiple signals in the local niche determine the fate of NSCs. These signals include: soluble factors (purple ovals) such as brain-derived neurotrophic factor (BDNF), cell-surface signals (yellow squares) such as Notch1, and extracellular matrix (ECM) factors such as laminin (pink triangles). Endothelial cells (EC) and astrocytes (AS) are thought to be supporting cells in the neurogenic niche, providing signals that are important for maintaining and mobilizing the NSC populations [2,74,119]. In the SVZ, type B cells resemble SGL type I cells. They express GFAP, nestin, Sox1, Sox2, BLBP and the astrocyte-specific L-glutamate L-aspartate transporter (GLAST). They give rise to GFAP-negative transit-amplifying type C cells, which then give rise to type A cells. Type A are PSA-NCAM- and DCX-expressing neuroblasts that migrate radially on 'glial tubes' in the rostral migratory stream (RMS) to layers in the olfactory bulb (OB) before terminal differentiation [108]. Abbreviations: cc, corpus callosum; hipp, hippocampus.

SGL and the SVZ, newly formed neurons have distinct physiological characteristics that could uniquely contribute to brain and behavioral plasticity [10–12].

Neurogenesis and learning and memory

Newly formed neurons are thought to play a role in brain function. In particular, the role of neurogenesis in olfaction and in hippocampal-dependent learning and memory seems to be multifaceted. Several approaches have been taken to elucidate the role of hippocampal neurogenesis in learning and memory (Box 1 for a summary of the methods used). It is crucial for the interpretation of the data obtained in these studies to consider the method of intervention (chemical, genetic, environmental), the type of neurogenic pathway involved, and its outcome for memory function (Box 2, Table S1 in the supplementary material online). For example, genetic manipulation of neurotrophin-3 affects spatial memory [13], whereas manipulation of presenilin-1 (PS1) affects contextual fear-conditioning [14]. Environmental enrichment [15] and running [16] produce increases in neurogenesis and enhanced performance on spatial memory tasks in multiple strains of mice [17]. Conversely, stress paradigms [18], irradiation [19–21] and the DNA methylating agent methylazoxy-methanol

Box 1. Neurogenesis and learning and memory: how do we make the connection?

Attempts to examine the relationship between neurogenesis and learning and memory have so far included:

(a) *Anti-mitotic drugs*. These would destroy proliferating neural progenitor cells, and any other proliferating cells in the brain (e.g. astrocytes). These drugs could affect quiescent NSCs to a lesser extent, as well as having potential secondary toxic effects on the parenchymal environment and its cellular residents (e.g. Ref. [22]).

(b) *Irradiation*. Low-dose irradiation would eliminate proliferating cells, but affect quiescent NSCs to a lesser extent (e.g. [24]). Thus, days or weeks after the irradiation, NPC populations would be replenished. Irradiation causes an inflammatory reaction that lasts for several weeks. This can cause secondary damage to neuronal populations and could affect the neurogenic microenvironments.

(c) *Expression of toxins driven by specific promoters*. Toxins driven by the promoters of genes that are active in NSC or neural progenitor cells (NPCs) would enable selective elimination of a subpopulation of these cells. Examples of such gene promoters are nestin, Sox2 and GFAP (e.g. Ref. [114]).

(d) *Expression of different genes driven by specific promoters*. This would affect specific signaling pathways regulating NSC biology and could change the course of neurogenesis (e.g. Ref. [115]).

(e) *Manipulation of the environment*. Includes physical exercise (running) and an enriched environment containing a running wheel (e.g. Ref. [69]).

(f) *Tailoring of learning and memory tests to the potential specific function of the dentate gyrus within the tri-synaptic hippocampal circuitry* (e.g. Box 2, Refs. [73,111]).

(g) *Tracing alterations in neurogenesis following behavioral training*. Nucleotide analogs or retrovirus-expressed fluorescent proteins can be used to label and trace NSCs, NPCs and/or their subpopulations (e.g. Ref. [116]).

acetate (MAM) [22] all decrease neurogenesis and impair different aspects of hippocampal-dependent memory (Box 2; Table S1 in the supplementary material online; see Ref. [23] for a review).

Although the role of neurogenesis in the SVZ is less clear, pioneering studies suggest that SVZ neurogenesis regulates synaptic plasticity in the olfactory bulb [24] and plays a functional role in olfaction ([25] for review). For example, a recent study suggests that both hippocampal and SVZ neurogenesis play a role in offspring recognition. Newly generated paternal olfactory interneurons were preferentially activated by offspring odors through prolactin signaling [26]. Likewise, male pheromone signatures induce neurogenesis in the SVZ and hippocampus of female mice [27]. Reinforcing an experience-based role for SVZ-neurogenesis in olfaction, another study suggests that exposure to male-soiled bedding, but not to its volatile compounds, increases the number of new neurons in the accessory olfactory bulb in mice [28]. Infusion of the antimitotic drug cytosine arabinoside (AraC) to the lateral ventricle abolished the arrival of newly born neurons into the olfactory bulb, resulting in decreased synchronized activity of mitral cells and impaired short-term olfactory memory [29]. In addition, long-term olfactory memory was found to be affected by focal irradiation of the SVZ, which decreased the rate of production of new olfactory bulb neurons [30]. Another study found that preventing cell death in the olfactory bulb (using a broad-spectrum caspase inhibitor) resulted in impaired odorant exploration and discrimination [34]), thus revealing an important role for neuronal turnover in the olfactory bulb.

Neurogenesis and aging

Both germinal centers, the SVZ and the SGL, exhibit an age-related decline in the production of new neurons [31]. The age-related decline in cell proliferation and new neurons in the SVZ has been linked to functional decline in olfaction in mice [32], and in the SGL is associated with decline in hippocampal-dependent spatial memory [31,33,34]. Despite an age-related reduction in the formation of new hippocampal neurons, the neurons that are added appear functionally equivalent to those in young brain [35,36]. This observation suggests that neurogenesis in the aged brain is not aberrant, but simply downregulated. In support, reduced cell proliferation in the DG and retarded neuronal maturation in the aging SGL were observed [37]. An interesting insight is provided by another study suggesting that the number of NSCs does not decline with aging, but that these cells exhibit increased quiescence [74] that could be due to decreased volume of the vascular niche [38]. Further support for the notion that changes in the neurogenic milieu take place in aging is provided by the observation that the level of key neurotrophic factors such as fibroblast growth factor-2 (FGF-2), insulin growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) are reduced in the aging hippocampus [39].

Maintenance of stem cell activity appears to be tightly controlled to prevent unregulated growth that could lead to cancer. Keeping stem cells out of the active cell-cycle phase and minimizing the risk of DNA damage could be especially important in aging and has led to a stem cell hypothesis of aging [1,40]. Tumor suppressor proteins, particularly $p16^{INK4a}$, have been shown to suppress stem cell activity in many aging stem cell populations [41–43]. Curiously, $p16^{INK4a}$ regulates stem cell activation in the SVZ, but not in the hippocampus [42], suggesting a fundamentally different regulatory mechanism is involved in the latter population. At this point it is not known whether a different stem cell autonomous regulatory mechanism is at work or whether control of activation is mediated through signals in the neurogenic niche within the aged hippocampus. An important question about the age-related decline in neurogenesis that remains unanswered concerns whether there is intrinsic suppression of NSC proliferation and maturation, or whether the decline is due to lack of trophic support and deficits in the neurogenic niche. Resolving which of these two regulatory mechanisms is involved, or whether there is a relative contribution of both elements, will be necessary for advancing therapeutic stimulation of aging NSCs.

Neurogenesis impairments in AD

Progressive memory loss and cognitive decline are the fundamental characteristics of AD. In addition, individuals afflicted with the disease experience difficulties in learning, speed of performance, recall accuracy and problem solving (see Ref. [44] for review). Impaired olfactory function (deficits in olfactory sensitivity, odor discrimination, and odor identification) appears to be one of the earliest detectable functional alterations in AD, and olfactory sen-

Box 2. Insight into the functional significance of adult hippocampal neurogenesis

It has long been known that the hippocampus is important for the acquisition of new memories [109]. However, the concept that different hippocampal subfields [dentate gyrus (DG), area CA1, area CA3] could make specific contributions to memory formation has been investigated only more recently [110]. The DG is considered important for spatial pattern separation, the ability to make fine spatial distinctions. Adult neurogenesis could be closely linked to this proposed function of the DG [73,111]. Using either a physiological model of newly born cell ablation, the natural decline of neurogenesis to very low levels in old mice [73], or elimination by X-irradiation in young mice, deficits in distinguishing between narrowly separated stimuli have been observed [73,111]. Figure I illustrates the role of neurogenesis elicited by physical exercise in promoting pattern separation.

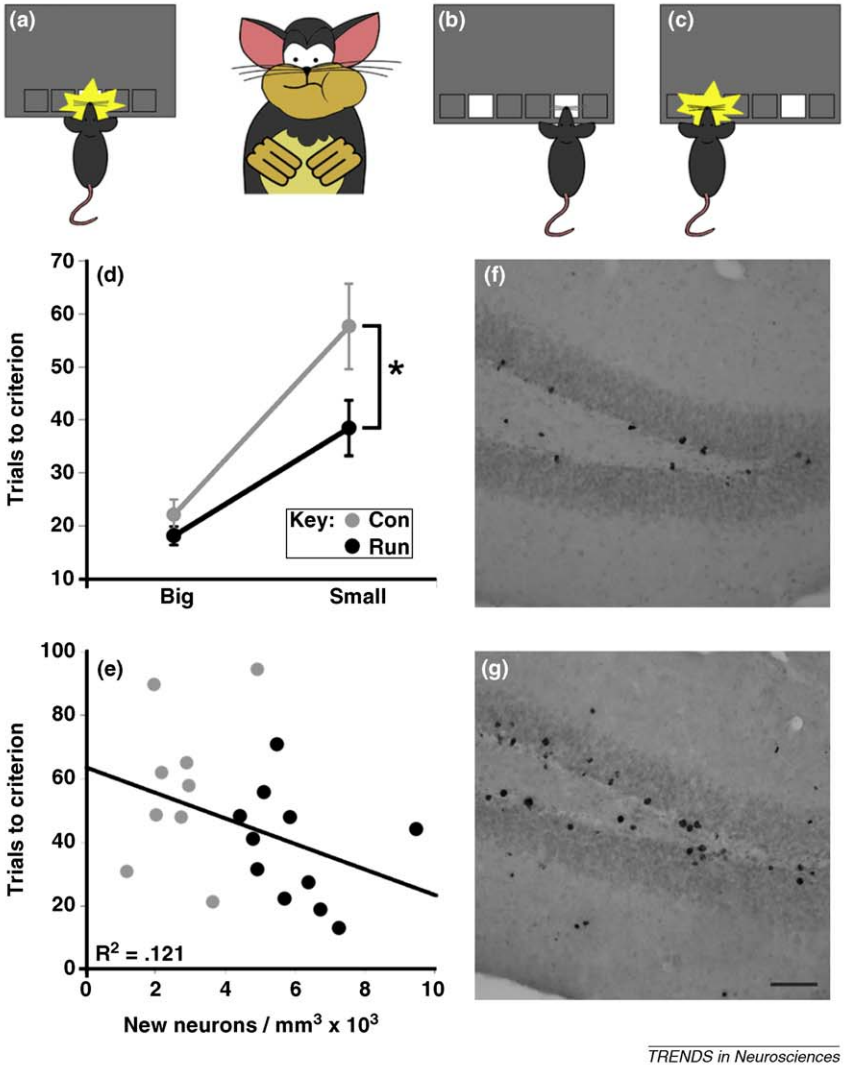

Figure I. Increased neurogenesis is associated with improved discrimination between the locations of two adjacent identical stimuli. **(a–c)** A mouse learns to choose between two similar objects when only one of the objects is reinforced with a food reward. **(a)** During the training phase mice learn to touch a screen for a food pellet reward. **(b)** Thereafter, mice were housed with or without a running wheel and learned to differentiate between a rewarded and non-rewarded icon. **(c)** The mouse chooses the correct (reinforced) icon and is rewarded with a food pellet. **(d)** Subsequently, sedentary and running mice were tested with either a large or small distance between two identical touchscreen icons. Mice were trained to reach a criterion of seven correct choices of the food-pellet rewarded trials out of a total of eight trials. Mice that were housed with a running wheel in their cage (run) performed better than controls (con) in the acquisition of the small separation (*, $P < 0.05$), but not the big separation condition ($P > 0.24$). **(e)** A trend towards a correlation between new neuron density in the DG and performance in the acquisition of the small separation was observed ($P = 0.13$). Photomicrographs of bromodeoxyuridine (BrdU)-positive cells in the DG of **(f)** control and **(g)** exercising mice ten weeks after the last injection of BrdU. BrdU is commonly used as a marker for dividing cells because it incorporates into the newly synthesized DNA of dividing cells during S phase, substituting for thymidine. Scale bar, 50 μm. Reproduced, with permission, from Ref. [73].

sitivity and olfactory discrimination could prove to be useful as predictors of cognitive decline [45,46].

Numerous studies employing different paradigms suggest that familial Alzheimer's disease (FAD)-linked transgenic mice exhibit impairments in learning and memory (see Ref. [47] for a review). These deficits include impairments in spatial reversal learning, acquisition of social recognition memory, acquisition of long-term spatial memory, utilization of spatial working memory, object recognition memory and contextual fear-conditioning. Deficits in olfaction in mouse models of AD have also been described (e.g. Refs. [48–50]) One working hypothesis is that impaired adult neurogenesis exacerbates memory deficits and impairs olfactory sensory perception in AD, possibly

by impairing hippocampal and olfactory neural circuits that support spatial memory and olfactory processing, respectively (see Ref. [51] for a review).

The neuropathological hallmarks of AD – senile plaques and neurofibrillary tangles – appear throughout the hippocampal formation and some regions of the cerebral cortex, and include both the SGL and SVZ neurogenic areas. Senile plaques are extracellular aggregates of amyloid β-peptide (Aβ) surrounded by dystrophic neurites. Aβ is liberated from a larger integral membrane protein APP (amyloid precursor protein) by the concerted action of β- and γ-secretases (see Ref. [44] for review). The vast majority of AD cases are the sporadic form of the disease. While the genetic cause for AD is not known, homozygosity for apolipoprotein E4 (*APOE4*) is the greatest risk factor after aging. Rare, familial, early-onset autosomal dominant FAD is caused by mutations in genes encoding *APP*, presenilins (*PS1*/*PSEN1* and *PS2*/*PSEN2*). Presenilins, as components of the aspartyl protease γ-secretase complex, cleave numerous membrane proteins within their membrane-spanning domains. Transgenic animals harboring mutant forms of APP and PS1 exhibit impaired neurogenesis in both SVZ and SGL early in life, and this begins prior to Aβ deposition and memory impairment [52]. In addition to Aβ, hyperphosphorylation and aggregation of tau within neurons could underlie some of these impairments [52]. Decreased neurogenesis is also observed in older FAD mice (e.g. Refs. [53,54]). Nevertheless, the extent of neurogenesis can either increase or decrease during the progression of symptoms as a response to the neurodegenerative process [55]. Studies examining neurogenesis in transgenic mice expressing single mutant variants of APP or PS1 have yielded conflicting observations (see below), possibly due to the different roles that APP and PS1 play in the regulation of adult neurogenesis (see Ref. [51] for review).

Physiological roles of APP and PS1 in neurogenesis

Although several studies have shown that transgenic mice expressing mutant APP or PS1 show impaired adult neurogenesis, little is known of the physiological role of either protein in neurogenesis. For example, APP is processed into three main fragments and all three proteolytic products have been shown to modulate neurogenesis differently. A soluble fragment of APP generated by α-secretase (sAPPα), exerts proliferative effects on embryonic NSC and also stimulates proliferation of progenitor cells in the adult SVZ [56]. The APP intracellular domain (AICD) generated by γ-secretase cleavage negatively modulates embryonic neurogenesis (possibly via binding to the Fe65 adapter protein) [57]. AICD also inhibits adult neurogenesis [58] by inducing proinflammatory changes in AICD-overexpressing transgenic mice [59]. Studies on the effects of Aβ, the third fragment produced by APP, on adult neurogenesis have produced conflicting results. Some studies found that Aβ negatively modulates neurogenesis, whereas other investigations reported that $A\beta_{42}$ (or oligomeric Aβ) stimulates adult SVZ neurogenesis in young but not old animals

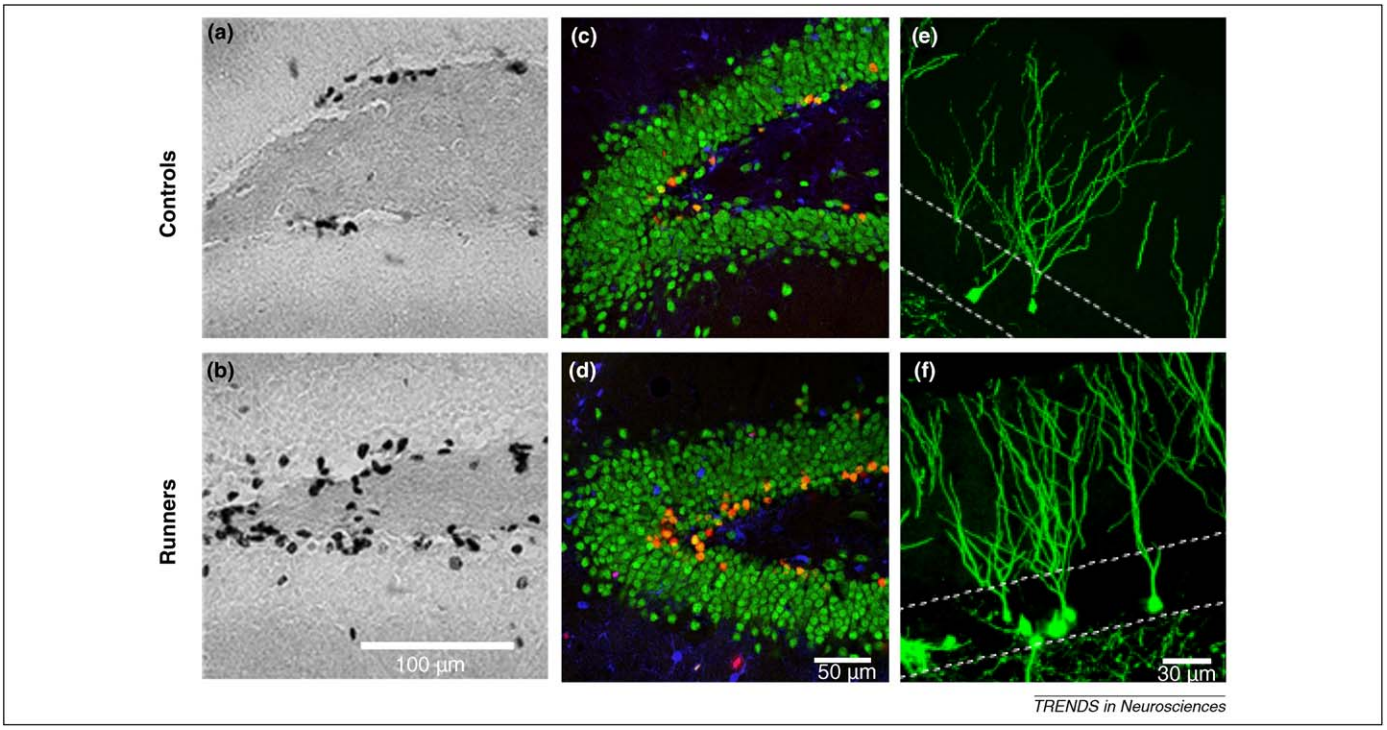

Figure 2. Regulation of cell proliferation and neurogenesis in the hippocampus by exercise. **(a,b)** Photomicrographs of bromodeoxyuridine (BrdU)-positive cells in the dentate gyrus (DG) of adult mice 1 day after the last of a series of 12 daily BrdU injections (50 mg/kg per day). Mice housed with a running wheel **(b)** have more BrdU+ cells than sedentary mice **(a)**, showing that running increases cell proliferation. **(c,d)** Confocal images of sections that were immunofluorescent-triple-labeled for BrdU (red), NeuN (green; an indicator of neuronal phenotype), and S100β (blue; selective for glial phenotype). Neurons double-labeled for BrdU+ (red) and NeuN+ (green) appear orange. These images demonstrate that cell survival and neuronal differentiation is enhanced four weeks after the last BrdU injection in runners (d) relative to control (c) mice. **(e,f)** Labeling using a retrovirus (which only integrates into dividing cells) was used to identify new neurons [112]. Retrovirus expressing green fluorescent protein (GFP) was injected into the DG of sedentary (e) and running (f) mice. Confocal images show more GFP+ new neurons in running mice compared to sedentary mice 4 weeks after virus injection. The dashed lines represent the boundaries of the granule cell layer of the DG. Reproduced, with permission, from Ref. [100].

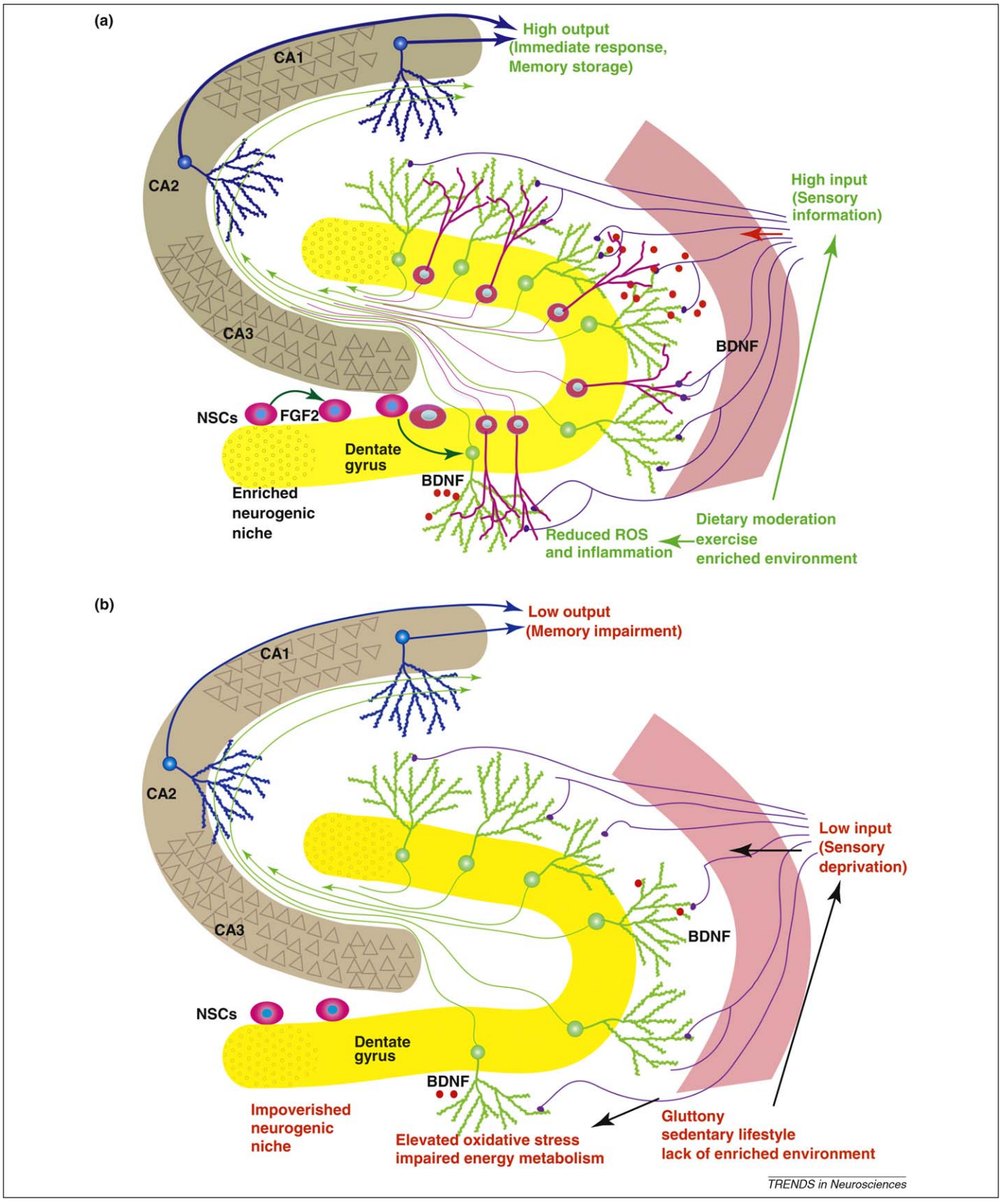

Figure 3. Healthy and unhealthy lifestyles may differentially affect hippocampal plasticity and cognitive aging. **(a)** A working model illustrating mechanisms by which a moderation of dietary energy intake, exercise and a cognitively challenging lifestyle can enhance hippocampal plasticity and sustain cognitive performance into late life. Exercise, dietary energy restriction and enrichment are considered to increase the activation of excitatory input to dendrites of granule neurons (green neurons) in the dentate gyrus. This synaptic activity induces the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and fibroblast growth factor 2 (FGF-2), which have multiple actions on neural stem cells (NSCs) and differentiated neurons that enhance hippocampal functional capability. FGF-2 enhances NSC proliferation. BDNF signaling increases the strength of potentiated synapses and also acts on NSCs to promote their survival and differentiation. By increasing neuronal network activity, healthy lifestyles can reduce levels of reactive oxygen species (ROS), hence reducing oxidative stress, and bolstering energy metabolism in hippocampal neurons and NSCs, thereby counteracting the aging process. **(b)** Mechanisms by which excessive energy intake and low levels of energy expenditure adversely affect neurogenesis and

([51] for detailed discussion). Recent studies suggest that an imbalance between inhibitory γ-aminobutyric (GABAergic) and excitatory glutamatergic neurotransmission could differentially impair neurogenesis in animal models of AD. Thus, in APOE4-knockin mice, presynaptic GABAergic input-mediated maturation of newborn neurons is diminished and potentiation of GABAergic signaling restores neurogenesis in these mice to normal levels [60]. In mice expressing mutant forms of APP (hAPP-J20), early inhibition of $GABA_A$ receptors to suppress GABAergic signaling or late inhibition of calcineurin for the enhancement of glutamatergic signaling normalizes neurogenesis [61].

The mechanisms underlying impaired neurogenesis in FAD mice expressing PS1 variants remain unclear. For example, conditional knockout of PS1 in the forebrains of adult mice resulted in decreased hippocampal neurogenesis in mice that were housed in an enriched environment [14]. This also caused subtle deficits in the performance of spatial memory behavioral tasks, such as the water maze [62]. Other studies confirmed that PS1 regulates the proliferation in adult neurogenesis that is triggered by enriched environment [63], possibly via a mechanism involving microglia [64]. Overexpression of wild-type PS1 was shown to promote adult neurogenesis, but FAD mutant PS1 failed to do so [65]. Similarly, mutant PS1 knockin (PS1-KI) mice exhibit decreased neurogenesis and impaired associative learning compared to wild-type mice [66]. By contrast, PS1-KO mice rescued with mutant PS1 exhibited increased proliferation of newly-born cells in the DG compared to mice rescued with wild-type PS1 [67]. This discrepancy might be attributed to the different genetic background of these mouse models. Nevertheless, these models are not fully adequate for examining the role of PS1 in adult neurogenesis because PS1 is either mutated or knocked down in large populations of neurons throughout the brain and not just in NPC populations. Such experimental limitations raise concerns about the relevance of these observations for neurogenesis specifically, and call for further examination of the role of PS1 in adult neurogenesis.

Modulation of neurogenesis by the environment in aging and in AD

Hippocampal neurogenesis can be regulated by environmental factors. In particular, environmental enrichment has been shown to be a positive regulator of adult neurogenesis [15]. Subsequent research revealed that the main neurogenic component of the enriched environment is physical activity (see Refs. [68,69] and Figure 2). Exercise-induced neurogenesis is correlated with improved learning and memory [16,68], possibly by modulation of bone morphogenetic protein (BMP) signaling [70,117]. Age-dependent reduction in neurogenesis can be partially prevented when animals are housed with a running wheel over a six-month period [71]. In addition, the decline in neurogenesis and cognition associated with normal aging can also be partially reversed by exercise (using a running wheel) that is initiated in 18-month-old mice [72], but not when initiated in very old mice (22 months old) [73], possibly due to loss of plasticity of rapid-amplifying type II progenitor cells [74].

Although the benefits of exercise and enrichment on neurogenesis and learning are apparent in young mice, the data in mouse models of AD are not as clear. Environmental enrichment has been reported to improve cognition in mouse models of AD [51], and to enhance neurogenesis and ameliorate neuropathology in some mouse models of AD [75]. However, environmental enrichment did not enhance neurogenesis in transgenic mice harboring FAD-linked PS1 variants [64] or in mice with conditional ablation of PS1 in the forebrain [14]. Subsequent research suggests that soluble factors released from microglia could be responsible for the lack of an effect of enrichment in FAD-linked PS1 mutant mice [64]. In other AD mouse models, such as APOE4 transgenic mice, enrichment reduced neurogenesis [76], whereas in the APP23 mouse (which expresses a human mutation in the APP gene; $hAPP_{751}$) it enhanced neurogenesis [77]. Taken together, these studies indicate that effects of environmental enrichment on adult neurogenesis vary greatly between the different mouse models of AD. This may depend in part on the opportunity for physical activity within the enriched environment. Indeed, several studies have reported beneficial effects of exercise on cognition, neurogenesis and amyloidosis in AD mouse models. In TgCRND8 mice (which express $APP_{695swe,Ind}$), exercise improved spatial memory and reduced extracellular Aβ plaque load [78]. Exercise was also found to be beneficial in Tg2576 mice (which express APP_{695swe}), even after the onset of pathology [79]. Similar to human studies on exercise, cognition, and *APOE* genotype [80], transgenic mice expressing APOE4 have been shown to benefit from regular physical activity [81]. Future experiments should determine the effect of exercise on FAD animal models exhibiting different aspects of AD pathology.

As with increased exercise, moderation in dietary energy intake can lead to improved energy metabolism, the promotion of neurogenesis and the protection of the brain against the adversities of aging (Figure 3a). Overeating, and the obesity and diabetes that result from excessive energy intake, are a major cause of morbidity and premature death that are rapidly spreading throughout the industrialized world. Epidemiological and clinical studies have provided evidence that individuals who overeat are at increased risk for cognitive impairment, particularly when they reach their 5^{th} and 6^{th} decades of life [82]. Excessive dietary energy (calorie) intake can impair hippocampal neurogenesis in rat and mouse models [83], whereas dietary energy restriction (DR) enhances hippocampal neurogenesis [84]. A high-energy diet could adversely affect neurogenesis and cognitive function by increasing levels of systemic stress (hyperactivation of the hypothalamic–pituitary–adrenal axis) and intrinsic oxidative and inflammatory stress in neurons,

cognitive function. Overeating/gluttony, physical inactivity and a cognitively impoverished lifestyle may result in suboptimal levels of input to the hippocampus. Low neuronal network activity in turn results in reduced levels of neurotrophic factors such as BDNF and FGF-2, as well as lower levels of neuroprotective protein chaperones and antioxidants. Consequently, NSC proliferation and differentiation into dentate granule neurons could be suppressed, and synapses can become dysfunctional and even degenerate. Elevated levels of oxidative and metabolic stress contribute to impaired synaptic plasticity and cognitive impairment. Diagram adapted from Ref. [113].

and by reducing the production of brain-derived neurotrophic factor (BDNF), protein chaperones and antioxidant enzymes [85,86] (Figure 3b). These adverse effects of a high-energy diet could be counteracted, at least in part, by exercise, which has been demonstrated to stimulate production of BDNF [85,118].

Modulation of neurogenesis as a therapeutic approach: minding the neurogenic niche

The studies described above imply that modulation of self-renewal, proliferation, migration and differentiation of endogenous NPCs could hold great promise for the maintenance of brain plasticity, the preservation of learning and memory capabilities, the prevention of aging-linked decline in neurogenesis, and for the repair of the diseased brain. A prerequisite for the modulation of neurogenesis is the identification of molecular targets regulating these processes. The neurogenic niche is thought to be a specialized microenvironment within the adult brain which has the capacity to sustain self-renewal of multipotent NSCs and promote their migration, as well as their differentiation into neurons and glia [87]. Adult NPCs derived from non-neurogenic areas exhibit self-renewal and multipotentiality once transplanted into a neurogenic brain area, and can differentiate in a region-specific context, suggesting that the microenvironment has a crucial role in providing and regulating fate-determining cues in the adult brain [88].

What makes the SVZ and SGL special in supporting the proliferation and differentiation of multipotent NPCs is an area of intensive investigation. It is postulated that endothelial cells and some specialized astrocytes provide a unique neurogenic niche and have the capability to promote proliferation and neuronal fate determination [89,90]. By contrast, astrocytes from non-neurogenic regions (e.g. the adult spinal cord) do not promote neuronal differentiation [90]. *In vivo* hot-spots of cell proliferation in the SGL are found to be in close proximity to capillaries and astrocytes [91,92]. It is thought that astrocytes in the neurogenic niche have a broad diversity of functions. For example, some behave like stem cells [92,93] and some provide neurogenic signals [90,94]. The neurogenic niche is believed to play a regulatory role in all steps of NPC maturation [95]. It is thought that the niche is comprised of soluble, membrane-tethered and extracellular matrix signaling molecules expressed by endothelial cells, GFAP-expressing NSC, NPCs, as well as by ependymal cells in the SVZ niche [96]. Progenitor cells actively interact with their microenvironment and have the capability to regulate it [90,97]. Numerous signaling pathways, some of which are developmental signals, are implicated in the regulation of adult neurogenesis. For example, epidermal growth factor (EGF) and FGF-2 have been shown to play a major role in the proliferation of progenitor cells. Wnt3 (wingless-type MMTV integration site family, member 3), TLX (protein tailless homolog, also known as NR2E1), Shh (sonic hedgehog), BMP antagonists, Notch, leukemia inhibitory factor, transforming growth factor-alpha and cytokines have also been shown to play a role in NPC proliferation and maintenance. Additional neurotrophic and growth factors such as BDNF, VEGF and the neurotransmitters GABA, glutamate and serotonin contribute significantly to the proliferation, differentiation and integration of new neurons into the existing circuitry (see Refs. [2,98] for reviews), whereas DCX and NCAM have been specifically implicated as being important factors involved in neuroblast migration. It is noteworthy that extensive migration capacity in amphibians and reptiles is thought to play a role in the high regenerative capacity of these organisms [99]. In the mammalian brain, migration of progenitors is widespread neonatally, and dramatically ceases with adulthood. Understanding the molecular processes that support neurogenesis would enable the enhancement of specific neurogenic processes and facilitate successful transplantation of stem cells into the brain.

Stem cell therapy for the aging brain

Given the age-related increase in burden of neurological diseases and injury, such as stroke, the idea of transplanting NPCs into the impaired aging brain has great appeal. As discussed above, despite the reduction in neurogenesis in the aged brain and the delayed maturation of the newly generated neurons, the aged hippocampus appears to retain sufficient environmental niche signals to support the normal maturation of new neurons. Indeed, there are a few reports describing cognitive improvement following transplantation of NPC into the aged hippocampus in both rats and humans [101,102]. Another relevant model is the transplantation of NPCs into the injured, aged hippocampus. A successful differentiation of NPCs grafted into the aged hippocampus was achieved in an excitotoxic injury model in rats [103]. However, in a cautionary observation of the future challenges to therapeutic use of stem cells in the aged brain, a quite low rate of efficiency in this process was noted compared to experience with grafts transplanted into the young hippocampus. It remains to be determined if the efficiency of neuronal differentiation can be augmented by priming the environment to modulate expression of some of the signaling factors discussed above. Interestingly, grafting of NPCs appears to stimulate endogenous neurogenesis within the aged hippocampus [104]. Notably, recent studies show that transplantation of NPCs into a mouse model of FAD rescues cognitive deficits in these mice [105] via BDNF signaling [106].

The goal of stem cell therapy would be to introduce new neurons that could contribute to functional enhancement or reconstruction of impaired neuronal circuitry. In this regard, it might not be necessary to transplant exogenous stem cells to achieve this aim. An alternative therapeutic strategy could be to enhance endogenous neurogenesis. As discussed above, neurogenesis in the aged brain can be stimulated by a variety of factors and the modulation of the neurogenic niche could be accomplished by elevating levels of the various proliferative and differentiation signals mentioned above. Such a recruitment strategy can be envisaged for the aged neurogenic regions within the hippocampus and olfactory bulb, but could prove more difficult for the greater portion of the cortical and subcortical structures where neurodegeneration can also occur during the aging process and in neurological disorders such as AD and stroke. Recruitment of endogenous neural stem/progenitor cells would then rely upon directed migration

Box 3. Outstanding Questions

- What is the significance of adult neurogenesis in relation to cognitive functions, and specifically in relation to the function of the DG and hippocampus, in humans?
- What are the molecular signals underlying neurogenesis in the adult brain?
- To what extent does deficient neurogenesis exacerbate cognitive impairments in humans with AD?
- Can recruited or grafted progenitor cells functionally contribute to circuitry in non-neurogenic regions of the brain, particularly on a background of aging and neurodegeneration?
- Is the aging-linked decline in neurogenesis comparable to stem cell decline in other organs?
- Is there a peripheral biomarker that could be used to detect reduced neurogenesis?

from the neurogenic regions or mobilization of the rare progenitor-like cells distributed throughout the brain parenchyma [107]. Given the overall reduction of neurogenic signals in the aged brain, such recruitment strategies for these other brain regions could be difficult to achieve.

Conclusion and future directions

The existence of neurogenic niches in the adult mammalian brain has initiated much hope for the use of NSCs for the therapy of the aging and diseased brain. Enhancement of brain plasticity, learning and memory, improved cognition and attenuation of neurodegeneration are only some of the high expectations of this therapy. Whether exogenous neural stem and/or progenitor cells are transplanted or endogenous cells are locally recruited, their successful survival, differentiation, and functional integration will be undertaken on a background of neurodegenerative pathology. Therapeutic stem cells will provide little benefit if they fall prey to the same pathology they are intended to reverse. Future experimental strategies will need to ascertain the extent of this risk and consider approaches to conditioning the environment into which the cells are placed to protect the new cells. Alternatively, the therapeutic cells might be themselves genetically modified to produce the appropriate conditioning signals. Successful implementation of these strategies will require a more complete understanding of the environmental signals necessary to foster successful neuronal differentiation, functional integration into neuronal circuits and protection against pathology (Box 3).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tins.2010.09.003.

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